Kam 09/869,916

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=> d his 1

     (FILE 'MEDLINE, HCAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     16:34:55 ON 24 FEB 2003)
L25          23 DUP REM L24 (26 DUPLICATES REMOVED)

=> d que l25
L1         3734 SEA KOHNO M?/AU
L2        40773 SEA WATANABE K?/AU
L3        44484 SEA L1 OR L2
L4           93 SEA L3 AND MICROTUBULE?
L5           54 SEA L3 AND ERK?
L6           86 SEA L3 AND MAP(3A) KINASE?
L7           12 SEA L4 AND (L5 OR L6)
L8          880 SEA MICROTUBULE#(5A) INTERFER?
L9          583 SEA TUBULIN#(5A)(POLYMERIZ? OR POLYMERIS?)(5A) INHIBITOR#
L10           1 SEA FILE=REGISTRY VINCRISTIN/CN OR VINCRISTINE/CN
L11          28 SEA FILE=REGISTRY ("DOLASTATIN 1"/CN OR "DOLASTATIN 10"/CN OR
                "DOLASTATIN 11"/CN OR "DOLASTATIN 12"/CN OR "DOLASTATIN 13"/CN
                OR "DOLASTATIN 13, 4-(3,4-DIHYDRO-6-HYDROXY-2-OXO-.ALPHA.-(PHEN
                YLMETHYL)-3-AMINO-1(2H)-PYRIDINEACETIC ACID)-"/CN OR "DOLASTATI
                N 13, 4-(3-AMINO-3,4-DIHYDRO-2-OXO-.ALPHA.-(PHENYLMETHYL)-1(2H)
                -PYRIDINEACETIC ACID)-"/CN OR "DOLASTATIN 14"/CN OR "DOLASTATIN
                 15"/CN OR "DOLASTATIN 16"/CN OR "DOLASTATIN 17"/CN OR
                "DOLASTATIN 17 (DOLABELLA AURICULARIA)"/CN OR "DOLASTATIN
                18"/CN OR "DOLASTATIN 2"/CN OR "DOLASTATIN 3"/CN OR "DOLASTATIN
                 4"/CN OR "DOLASTATIN 5"/CN OR "DOLASTATIN 6"/CN OR "DOLASTATIN
                 7"/CN OR "DOLASTATIN 8"/CN OR "DOLASTATIN 9"/CN OR "DOLASTATIN
                 A"/CN OR "DOLASTATIN B"/CN OR "DOLASTATIN C"/CN OR "DOLASTATIN
                 D"/CN OR "DOLASTATIN E"/CN OR "DOLASTATIN G"/CN OR "DOLASTATIN
                 H"/CN OR "DOLASTATIN I"/CN)
L12       94136 SEA L10 OR VINCRIST?
L13        1177 SEA DOLASTATIN? OR L11
L14         968 SEA ERK?(3A) MAP?(3A) KINASE#(5A) INHIBITOR?
L15          25 SEA ERK?(3A) MAP?(3A) CASCADE#(5A) INHIBITOR?
L16        9788 SEA MAP?(5A) KINASE#(7A) INHIBITOR?
L17        2957 SEA ERK?(5A) KINASE#(5A) INHIBITOR?
L18        6359 SEA MAPK (5A) INHIBITOR?
L19       77645 SEA MITOGEN(3A) ACTIVATED(3A) PROTEIN?(5A) KINASE#
L20        7556 SEA L19(7A) INHIBITOR?
L21       96466 SEA L8 OR L9 OR L12 OR L13
L22       18180 SEA (L14 OR L15 OR L16 OR L17 OR L18) OR L20
L23          38 SEA L21 AND L22
L24          49 SEA L7 OR L23
L25          23 DUP REM L24 (26 DUPLICATES REMOVED)


=> d ibib abs 125 1-23

L25  ANSWER 1 OF 23  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        2002:977582  HCAPLUS
DOCUMENT NUMBER:         138:37450
TITLE:                   Ras-MEK-ERK1/2 signaling pathway in the production of
                         inflammatory and neuropathic pain and uses for
                         analgesic screening
INVENTOR(S):             Levine, Jon David; Messing, Robert O.
PATENT ASSIGNEE(S):      The Regents of the University of California, USA
SOURCE:                  PCT Int. Appl., 134 pp.
                         CODEN: PIXXD2

                    Search completed by David Schreiber   308-4292
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Kam 09/869,916

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002102232	A2	20021227	WO 2002-US19107	20020614

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003008807	A1	20030109	US 2002-173332	20020614

PRIORITY APPLN. INFO.: US 2001-298491P P 20010614

AB This invention pertains to the discovery of a novel pathway that mediates hyperalgesia, neuropathic pain, and inflammatory pain. This pathway is a third independent pathway that involves activation of extracellular signal-regulated kinases (ERKs) 1 and 2. The pathway comprises a Ras-MEK-ERK1/2 cascade that acts independent of PKA or PKC.epsilon. as a novel signaling pathway for the prodn. of inflammatory (and neuropathic) pain. This pathway presents numerous targets for a new class of analgesic agents.

L25 ANSWER 2 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:594822 HCAPLUS
DOCUMENT NUMBER: 137:154857
TITLE: Preparation of nicotinamide biaryl derivatives as inhibitors of PDE4 isozymes
INVENTOR(S): Chambers, Robert James; Magee, Thomas Victor; Marfat, Anthony
PATENT ASSIGNEE(S): Pfizer Productors Inc., USA
SOURCE: PCT Int. Appl., 224 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060875	A1	20020808	WO 2001-IB2341	20011206

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002193612	A1	20021219	US 2002-62813	20020131

PRIORITY APPLN. INFO.: US 2001-265492P P 20010131
OTHER SOURCE(S): MARPAT 137:154857
GI

Search completed by David Schreiber 308-4292

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; g = 0-1; j = 0-1; provided that when j = 0, n must be 2; k = 0-1; m = 0-2; n = 1-2; W1 = 0, SOt (t = 0-2), NR3; W2 = OCR9R10, or absent; Y = CR1, NOk (k = 0-1); R9, R10 = H, F, CF3, etc.; or R9 and R10 are taken together, but only in the case where m = 1, to form a spiro moiety; R7, R8 have the same meaning as R9, R10 except that one of them must be H; R1, R2 = H, F, Cl, etc.; R3 = H, alkyl, Ph, etc.; R4-R6 = H, F, Cl, etc.; Q1 = Ph, benzodioxyl, etc.; Q2 = biaryl moiety], useful as inhibitors of PDE4 in the treatment of diseases regulated by the activation and degranulation of eosinophils, esp. asthma, chronic bronchitis, and chronic obstructive pulmonary disease, were prepd. E.g., a multi-step synthesis of the amide II, starting from Me 3-bromobenzoate and 4-formylbenzeneboronic acid, was given. Compds. I showed anti-inflammatory activity at 0.0001 .mu.M to 20.0 .mu.M in whole blood assay for LTE4.

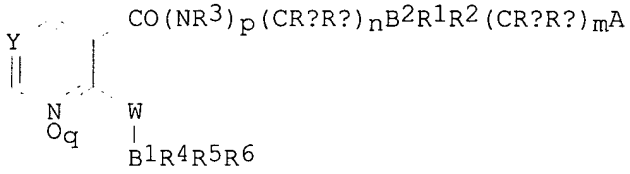
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:591707 HCAPLUS
DOCUMENT NUMBER: 137:140509
TITLE: Preparation of nicotinamides and mimetics as inhibitors of phosphodiesterase IV isozymes
INVENTOR(S): Chambers, Robert J.; Magee, Thomas V.; Marfat, Anthony
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 180 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1229034	A1	20020807	EP 2002-250202	20020111
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002111495	A1	20020815	US 2002-62811	20020131
BR 2002000250	A	20021008	BR 2002-250	20020131

PRIORITY APPLN. INFO.: US 2001-265240P P 20010131
US 1997-43403P P 19970404
US 1998-105120P P 19981021
OTHER SOURCE(S): MARPAT 137:140509
GI

Search completed by David Schreiber 308-4292



I

AB Title compds. [I; p, q = 0, 1; m = 0-2; n = 1, 2; A = CO2R7, CONR9CO2R7, CONR7R9, OP(O)(OH)2, SO3H, acylsulfonamido, etc.; W = O, S, SO, SO2, NR3; Y = N, NO, CR11; R1, R2 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, etc.; R3 = H, alkyl, Ph, PhCH2, etc.; R4-R6 = H, F, Cl, alkynyl, cyano, NO2, etc.; R7 = H, (substituted) alkyl, alkenyl, alkynyl; R9 = H, alkyl, cycloalkyl, Ph, PhCH2, pyridyl, etc.; R11 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, fluoroalkoxy, etc.; Ra, Rb = H, F, CF3, alkyl, (substituted) cycloalkyl, Ph, PhCH2; B1, B2 = 3-7 membered (hetero)cyclyl, 7-12 membered poly(hetero)cyclyl; pairs of variables may form rings; with provisos], were prepd. (no data). Thus, Me 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionate was suspended in Me3COH. Aq. NaOH was added to the suspension, and the reaction mixt. was refluxed 1 h to give 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionic acid.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 4 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:622105 BIOSIS
DOCUMENT NUMBER: PREV200200622105
TITLE: Benzoheterocycles and their uses as MEK inhibitors.
AUTHOR(S): Barrett, Stephen (1); Tecle, Haile; Bridges, Alexander J.
CORPORATE SOURCE: (1) Livonia, MI USA
ASSIGNEE: Warner-Lambert Company
PATENT INFORMATION: US 6469004 October 22, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Oct. 22, 2002) Vol. 1263, No. 4, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB The invention provides compounds having formula (I), wherein W is OH, or derivatives of the carboxylic acid, and Q is a heterocyclo-condensed ortho-phenylene residue. These compounds are useful as MEK inhibitors, particularly in the treatment of proliferative diseases such as cancer. ##STR1##

L25 ANSWER 5 OF 23 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002371895 EMBASE
TITLE: Agents targeting Ras signaling pathway.
AUTHOR: Dancey J.E.
CORPORATE SOURCE: J.E. Dancey, Cancer Therapy Evaluation Program, National Cancer Institute, 6130 Executive Blvd, Rockville, MD 20852, United States. danceyj@ctep.nci.nih.gov
SOURCE: Current Pharmaceutical Design, (2002) 8/25 (2259-2267). Refs: 63
ISSN: 1381-6128 CODEN: CPDEFP

Search completed by David Schreiber 308-4292

Kam 09/869,916

COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Ras genes encode proteins that activate in an intracellular signaling network controlling differentiation, proliferation and cell survival. Mutated Ras oncogenes encoding proteins that are constitutively active can induce malignancies in a variety of laboratory models. In human malignancies, Ras mutations are common, having been identified in approximately 30% of cancers. Given the importance of Ras and downstream targets Raf and MEK in the development of malignancies and their frequent expression in human cancers, it is not surprising that a variety of agents disrupting signaling through Ras and downstream proteins are under development. These agents can be broadly classified structurally as small molecules and anti-sense oligonucleotides. They can be characterized functionally as those inhibiting Ras protein expression such as the oligodeoxynucleotide ISIS 2503, those inhibiting Ras processing, in particular the farnesyl transferase inhibitors R115777, SCH 66336 and BMS 214662, and those inhibiting downstream effectors Raf, such as ISIS 5132 and MEK, which is inhibited by CI-1040. The purpose of this review is to highlight recent advances in the development of these agents.

L25 ANSWER 6 OF 23 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002456340 EMBASE
TITLE: Inhibitors of the ras oncogene as therapeutic targets.
AUTHOR: Ghobrial I.M.; Adjei A.A.
CORPORATE SOURCE: Dr. A.A. Adjei, Division of Medical Oncology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, United States. adjei.alex@mayo.edu
SOURCE: Hematology/Oncology Clinics of North America, (2002) 16/5 (1065-1088).
Refs: 156
ISSN: 0889-8588 CODEN: HCNAEQ
PUBLISHER IDENT.: S 0889-8588(02)00050-3
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Advances in our understanding of the molecular pathways and genetic mutations that control tumor cell proliferation and metastasis present an opportunity to develop novel, mechanism-based therapeutic strategies. Ras mutations are the most frequently activated oncogenes in human tumors, with over 30% expressing ras mutations. Molecular dissection of the signaling pathway and the mechanisms of ras anchorage, post-translational modification, and downstream effector signaling of ras now under intensive investigation will help us to design additional methods for ras-directed therapy in an effort to reach an optimal treatment for human tumors that will most likely comprise a combination of modalities targeted at the different underlying genetic defects. The successes and limitations of ras-targeted therapies must be viewed in light of the increasing

Search completed by David Schreiber 308-4292

understanding of the complexity of the ras-signaling pathway. Only now are we beginning to discover the many functions of this integrated pathway, such as the differences between the actions of various ras isoforms that may affect our choice of therapeutic approach. Many of these Ras therapeutic targets have shown success in preclinical studies, and some have shown efficacy in clinical trials with minimal toxicities. Compounds that block ras-transforming activity without affecting normal ras function seem more attractive for the future development of ras-targeted therapy. FTIs may partially fulfill such requirements. Based on their specific, novel, and mechanism-based action; minimal toxicity; and encouraging responses in clinical trials, the development of Ras therapeutic targets as single agents or in combination with conventional chemotherapy and radiotherapy should be pursued.

L25 ANSWER 7 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:409167 BIOSIS
DOCUMENT NUMBER: PREV200200409167
TITLE: Blockade of the extracellular signal-regulated kinase pathway enhances the antitumor activity of **microtubule**-depolymerizing agents in tumor cells in which the pathway is constitutively activated.
AUTHOR(S): **Watanabe, Kazushi (1)**; Noda, Shinji (1); Iwashita, Ken-ichi (1); Tanimura, Susumu (1); Ozaki, Kei-ichi (1); **Kohno, Michiaki (1)**
CORPORATE SOURCE: (1) Laboratory of Cell Regulation, School of Pharmaceutical Sciences, Nagasaki University, Nagasaki Japan
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 583-584. print. Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

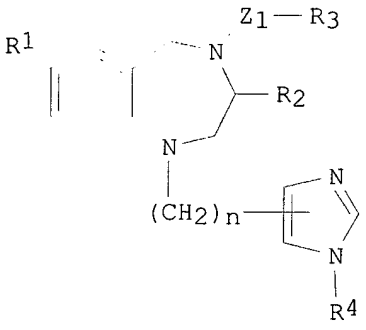
L25 ANSWER 8 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:730715 HCAPLUS
DOCUMENT NUMBER: 135:288636
TITLE: Synergistic methods and compositions for treating cancer using two or more anticancer agents
INVENTOR(S): Lee, Francis Y.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001072721	A2	20011004	WO 2001-US9193	20010322
WO 2001072721	A3	20020613		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

Search completed by David Schreiber 308-4292

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
EP 1272193 A2 20030108 EP 2001-920653 20010322
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
US 2002002162 A1 20020103 US 2001-817456 20010326
NO 2002004610 A 20021125 NO 2002-4610 20020926
PRIORITY APPLN. INFO.: US 2000-192278P P 20000327
WO 2001-US9193 W 20010322
OTHER SOURCE(S): MARPAT 135:288636
GI



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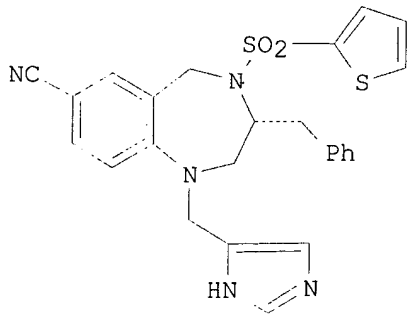

II

AB The present invention provides a synergistic method for the treatment of cancer which comprises administering a synergistically, therapeutically effective amt. of: (i) at least agent selected from the group consisting of cytotoxic agents and cytostatic agents, and (ii) a compd. of formula [I; R1 = Cl, Br, CN, substituted Ph, substituted pyridyl; R2 = alkyl, aralkyl; R3,R5 = substituted alkyl, aryl, heterocycle; R4 = H, alkyl; Z1 = CO, SO2, CO2, SO2N(R5); n = 1,2] or a pharmaceutically acceptable salt thereof. The present invention further provides a pharmaceutical compn. for the synergistic treatment of cancer which comprises at least one agent selected from the group consisting of antiproliferative cytotoxic agents and antiproliferative cytostatic agents, a compd. of formula I, and a pharmaceutically acceptable carrier. Synergism was obsd. when non-proliferating tumor cells were treated with diazepine II.cntdot.HCl and paclitaxel (III) simultaneously or when III preceded II.cntdot.HCl.

L25 ANSWER 9 OF 23 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001184212 MEDLINE
DOCUMENT NUMBER: 21139090 PubMed ID: 11245462
TITLE: Inhibition of extracellular signal-regulated kinase (ERK) mediates cell cycle phase independent apoptosis in vinblastine-treated ML-1 cells.
AUTHOR: Stadheim T A; Xiao H; Eastman A
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, New Hampshire 03755, USA.
CONTRACT NUMBER: CA50224 (NCI)
F32 CA86476 (NCI)
T32 CA09658 (NCI)
SOURCE: CANCER RESEARCH, (2001 Feb 15) 61 (4) 1533-40.

Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329

AB Chemotherapeutic agents induce alterations in intracellular signal transduction cascades that culminate in the initiation of the apoptotic program. Here, the relationship between the mitogen-activated protein kinase (MAPK) response and apoptosis in ML-1 cells treated with vinblastine and paclitaxel was investigated. We show that these compounds elicit different effects on MAPKs with vinblastine, but not paclitaxel, increasing both c-Jun-NH2-terminal kinase (JNK) and p38 activity. However, vinblastine and paclitaxel both induced apoptosis with similar kinetics, suggesting that increased JNK and p38 activity is not required for apoptosis that is induced by **microtubule interfering** agents. Strikingly, the abrogation of extracellular signal-regulated **kinase** (**ERK**)-signaling by the **MAPK/ERK** **kinase** (MEK)1/2 **inhibitor** PD098059 in combination with vinblastine robustly induced apoptosis in ML-1 cells at a rate much faster than treatment with vinblastine alone and occurred at all phases of the cell cycle. This apoptotic induction was attributed to JNK activation because: (a) non-JNK-activating concentrations of vinblastine failed to increase apoptosis in the presence of PD098059; (b) apoptosis induced by paclitaxel, which did not activate JNK, was not potentiated by PD098059; and (c) transduction of an inhibitor of JNK activity partially suppressed both JNK activity and apoptosis induced by vinblastine plus PD098059. Additionally, we found that the activation of JNK by vinblastine occurred upstream of effector caspase activation because treatment with a pan-specific caspase inhibitor (valine-alanine-aspartate-fluoromethylketone) resulted in complete abrogation of apoptosis with no effect on MAPK signaling. Taken together, these data suggest that inhibition of the MEK-->ERK signal transduction cascade alleviates cell cycle dependence for vinblastine-induced apoptosis by a mechanism that requires JNK activation.

L25 ANSWER 10 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:289938 BIOSIS
DOCUMENT NUMBER: PREV200100289938
TITLE: Norepinephrine-induced translocation of cytosolic phospholipase A2 to the nuclear envelope via the mitogen-activated protein kinase pathway requires actin filament polymerization in rabbit vascular smooth muscle cells.
AUTHOR(S): Fatima, Soghra (1); Khandekar, Zinat (1); Malik, Kafait (1)
CORPORATE SOURCE: (1) University of Tennessee, 874 Union Avenue, Memphis, TN, 38163 USA
SOURCE: FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A542. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Cytoskeletal structures are known to be involved in the trafficking of various cellular proteins. This study was conducted to investigate the contribution of actin filaments to cytosolic phospholipase A2 (cPL >2) translocation to the nuclear envelope elicited by norepinephrine (NE) in rabbit aortic smooth muscle cells (VSMC). NE (10 muM) caused cPLA2 accumulation around the nuclear envelope as determined from its immunofluorescence. cPLA2 translocation was blocked by an inhibitor of actin filament polymerization (cytochalasin D, 15 muM) but not by colchicine (10 muM), an **inhibitor** of **tubulin polymerization**. An **inhibitor** of **mitogen-activated protein kinase** (**MAPK**) **kinase** (MEK) activity (PD98059) and antisense **MAPK** oligonucleotides (5'-AGCCGCCGCCGCCGCCGCCAT-3' 5 muM) disrupted actin filament polymerization and NE-induced cPLA2 translocation to the nuclear envelope, whereas sense and scrambled MAPK oligonucleotides (5'-ATGGCGGCGGCGGCGGCGGCT-3' 5 muM, 5'-GCACAGCCGCCTGCCGCCGCC-3' 5 muM) had no effect. These data suggest that NE-induced translocation of cPLA2 to the nuclear envelope requires intact actin filaments and that MAPK plays an important role in maintaining actin in its polymerized form and facilitating the translocation of cPLA2 to the nuclear envelope in rabbit VSMC.

L25 ANSWER 11 OF 23 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002251996 MEDLINE
DOCUMENT NUMBER: 21985018 PubMed ID: 11989653
TITLE: Reversal effect of specific inhibitors of extracellular-signal regulated protein kinase pathway on P-glycoprotein mediated **vincristine** resistance of L1210 cells.
AUTHOR: Kisucka J; Barancik M; Bohacova V; Breier A
CORPORATE SOURCE: Institute for Heart Research, Slovak Academy of Sciences, Bratislava, Slovakia.
SOURCE: GENERAL PHYSIOLOGY AND BIOPHYSICS, (2001 Dec) 20 (4) 439-44.
Journal code: 8400604. ISSN: 0231-5882.
PUB. COUNTRY: Slovakia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020507
Last Updated on STN: 20020611
Entered Medline: 20020610

AB Effect of specific **inhibitors** of extracellular-signal regulated protein **kinase** (**ERK**) pathway, PD98059 and U0126, on P-glycoprotein (Pgp)-mediated **vincristine** resistance of L1210/VCR cells was investigated. Both test inhibitors significantly reduced the survival of L1210/VCR cells in the presence of **vincristine** and this was associated with a decrease of LC50 values to **vincristine** from 2.65+/-0.43 to 0.67+/-0.28 micromol/l and to 0.69+/-0.09 micromol/l after treatment with 50 micromol/l PD98059 and 25 micromol/l U0126, respectively. Moreover, the effects of PD98059 are connected also with an increased intracellular accumulation of radiolabeled **vincristine** in resistant L1210/VCR cells in concentration dependent manner. The results of this study demonstrate that inhibitors of ERK signaling pathway are reversal agents of **vincristine** resistance in L1210/VCR cells. The precise mechanism of PD98059 and U0126 action in modulation of MDR is not resolved yet, but the role of ERK-mediated phosphorylation cascade could be considered.

Search completed by David Schreiber 308-4292

L25 ANSWER 12 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:241873 HCAPLUS
DOCUMENT NUMBER: 134:216717
TITLE: **Microtubule interfering** agents
AUTHOR(S): **Watanabe, Kazushi; Kohno, Michiaki**
CORPORATE SOURCE: Lab. Cell Regul., Sch. Pharm. Sci., Nagasaki Univ., Japan
SOURCE: Saishin Igaku (2001), 56(3), 390-397
CODEN: SAIGAK; ISSN: 0370-8241
PUBLISHER: Saishin Igakusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 14 refs., on antitumor activities of **microtubule interfering** agents and its mechanism, discussing enhancement of antitumor activity (apoptosis induction) by combination of tubulin polymn. **inhibitors** and **ERK-MAP kinase cascade** blocking agents, roles of Rho and PLC.beta. in apoptosis signaling induced by tubulin polymn. inhibitors, and useful application of **microtubule interfering** agents to tumor chemotherapy.

L25 ANSWER 13 OF 23 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001350723 EMBASE
TITLE: Differentiation therapy of human cancer: Basic science and clinical applications.
AUTHOR: Leszczyniecka M.; Roberts T.; Dent P.; Grant S.; Fisher P.B.
CORPORATE SOURCE: P.B. Fisher, Herbert Irving Compreh. Cancer Ctr., Columbia University, College of Physicians and Surgeons, New York, NY 10032, United States. pbfl@columbia.edu
SOURCE: Pharmacology and Therapeutics, (2001) 90/2-3 (105-156). Refs: 730
ISSN: 0163-7258 CODEN: PHTHDT
PUBLISHER IDENT.: S 0163-7258(01)00132-2
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Current cancer therapies are highly toxic and often nonspecific. A potentially less toxic approach to treating this prevalent disease employs agents that modify cancer cell differentiation, termed 'differentiation therapy.' This approach is based on the tacit assumption that many neoplastic cell types exhibit reversible defects in differentiation, which upon appropriate treatment, results in tumor reprogramming and a concomitant loss in proliferative capacity and induction of terminal differentiation or apoptosis (programmed cell death). Laboratory studies that focus on elucidating mechanisms of action are demonstrating the effectiveness of 'differentiation therapy,' which is now beginning to show translational promise in the clinical setting.

L25 ANSWER 14 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
ACCESSION NUMBER: 2001:232286 BIOSIS

Search completed by David Schreiber 308-4292

Kam 09/869,916

DOCUMENT NUMBER: PREV200100232286
TITLE: Signal transduction pathway of multidrug resistance (mdr) gene expression in human monocytic cells.
AUTHOR(S): Kim, Jung Ok; Suh, Jang Soo; Lee, Young Sup (1)
CORPORATE SOURCE: (1) Department of Biochemistry, College of Natural Sciences, Kyungpook National University, Taegu, 702-701: yselee@kyungpook.ac.kr South Korea
SOURCE: Korean Journal of Genetics, (March, 2001) Vol. 23, No. 1, pp. 103-109. print.
ISSN: 0254-5934.
DOCUMENT TYPE: Article
LANGUAGE: Korean
SUMMARY LANGUAGE: English

AB Two prominent members of the ATP-binding cassette superfamily of transmembrane proteins, multidrug resistance (mdr) P-glycoprotein and multidrug resistance associated protein (mrp), can mediate the cellular extrusion of xenobiotics and anticancer drugs from cells. mdr and mrp gene expressions of a human monocytic HL60 cell were investigated by using reverse transcription polymerase chain reaction. mrp gene was constitutively expressed in HL60 cells. However, treatment of HL60 cells with retinoic acid (RA) or phorbol ester (PMA) induced mdr expression and showed resistance to adriamycin- or **vincristine**-induced cell death. RT-PCR analyses revealed that mdr expression induced by PMA or RA were suppressed in cells treated with protein kinase C (PKC) or NFkappaB **inhibitor**. RA activated extracellular signal-regulated **kinase mitogen-activated protein** (**MAP**) **kinase** and ribosomal S6 **kinase**, but not p38 and JNK MAP kinase. Gel shift and supershift analyses with nuclear extracts indentified the activation of p50 NFkappaB subunit which was induced by RA. These results suggested that mdr gene expression in HL60 cells was mediated by PKC/NFkappaB signal pathways.

L25 ANSWER 15 OF 23 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001465140 MEDLINE
DOCUMENT NUMBER: 21349901 PubMed ID: 11457647
TITLE: SB203580, a specific **inhibitor** of p38-**MAPK** pathway, is a new reversal agent of P-glycoprotein-mediated multidrug resistance.
AUTHOR: Barancik M; Bohacova V; Kvackajova J; Hudecova S; Krizanova O; Breier A
CORPORATE SOURCE: Institute for Heart Research, Slovak Academy of Sciences, Dubravska cesta 9, 842 33, Bratislava, Slovak Republic.
SOURCE: EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, (2001 Aug) 14 (1) 29-36.
Journal code: 9317982. ISSN: 0928-0987.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010821
Last Updated on STN: 20011022
Entered Medline: 20011018

AB P-glycoprotein (P-gp) is the plasma membrane transport pump responsible for efflux of chemotherapeutic agents from cells and is one of the systems that secures multidrug resistance (MDR) of neoplastic cells. In the present study, drug sensitive L1210 and multidrug resistant L1210/VCR (characterized by overexpression of P-gp) mouse leukemic cell lines were used as an experimental model. We have found that SB203580, a specific

Search completed by David Schreiber 308-4292

inhibitor of p38-**MAPK** pathway, significantly reduced the degree of the **vincristine** resistance in L1210/VCR cells. This phenomenon was accompanied by a decrease in the LC(50) value of **vincristine** from 3.203+/-0.521 to 0.557+/-0.082 microM. The LC(50) value of sensitive cells for **vincristine** was about 0.011 microM. The effect of SB203580 on L1210/VCR cells was associated with significantly increased intracellular accumulation of [3H]-**vincristine** in the concentration dependent manner. Prolonged exposure of resistant cells to 30 microM SB203580 did neither significantly influence the gene expression of P-gp, nor change the protein levels of p38-MAPK. Western blot analysis revealed that the MDR phenotype in L1210/VCR cells was associated with increased level and activity of cytosolic p38-MAPK. In resistant cells, the enhanced phosphorylation of both, p38-MAPK and ATF-2 (endogenous substrate for p38-MAPK) was found as well. In conclusion we could remark that SB203580, an inhibitor of p38 kinase pathway, reversed the MDR resistance of L1210/VCR cells. MDR phenotype of these cells is connected with increased levels and activities of p38-MAPK. These findings point to the possible involvement of the p38-MAPK pathway in the modulation of P-gp mediated multidrug resistance in the L1210/VCR mouse leukemic cell line. However, the mechanisms of SB203580 action should be further investigated.

L25 ANSWER 16 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:475559 HCAPLUS
DOCUMENT NUMBER: 133:94552
TITLE: Antitumor agents
INVENTOR(S): **Kohno, Michiaki; Watanabe, Kazushi**
PATENT ASSIGNEE(S): Teikoku Hormone Mfg. Co., Ltd., Japan
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000040268	A1	20000713	WO 2000-JP2	20000104
W: AU, CA, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2358491	AA	20000713	CA 2000-2358491	20000104
EP 1142583	A1	20011010	EP 2000-900040	20000104
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: JP 1999-2971 A 19990108
WO 2000-JP2 W 20000104

AB When an antitumor agent acting on **microtubule** is used together with an **ERK MAP kinase** cascade blocking agent, the antitumor effect of the agent acting on **microtubule** can be remarkably potentiated. Namely, a combination of the agent acting on **microtubule** with the **ERK MAP kinase** cascade blocking agent is useful as an excellent antitumor agent with a remarkable efficacy. Injection solns. were formulated contg. TZT-1027 0.2 mg and isotonic NaCl soln. q.s./ampule and were used in combination with tablets contg. an **ERK MAP kinase** cascade blocking agent.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 17 OF 23 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000270181 MEDLINE
DOCUMENT NUMBER: 20270181 PubMed ID: 10809726
TITLE: **Microtubule-interfering** agents stimulate the transcription of cyclooxygenase-2. Evidence for involvement of ERK1/2 AND p38 mitogen-activated protein kinase pathways.
AUTHOR: Subbaramaiah K; Hart J C; Norton L; Dannenberg A J
CORPORATE SOURCE: Department of Medicine, New York Presbyterian Hospital-Cornell and Strang Cancer Prevention Center, New York, New York 10021, USA.. ksubba@mail.med.cornell.edu
CONTRACT NUMBER: S/G 2P01 CA68425 (NCI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 May 19) 275 (20) 14838-45.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000621

AB We investigated whether **microtubule-interfering** agents (MIAs: taxol, colchicine, nocodazole, vinblastine, **vincristine**, 17-beta-estradiol, 2-methoxyestradiol) altered cyclooxygenase-2 (COX-2) expression in human mammary epithelial cells. MIAs enhanced prostaglandin E(2) synthesis and increased levels of COX-2 protein and mRNA. Nuclear run-off assays revealed increased rates of COX-2 transcription after treatment with MIAs. Calphostin C, an inhibitor of protein kinase C, blocked the induction of COX-2 by MIAs. The stimulation of COX-2 promoter activity by MIAs was inhibited by overexpressing dominant negative forms of Rho and Raf-1. MIAs stimulated ERK, JNK, and p38 **mitogen-activated protein kinases** (**MAPK**); pharmacological **inhibitors** of **MAPK kinase** and p38 **MAPK** blocked the induction of COX-2 by MIAs. Overexpressing dominant negative forms of ERK1 or p38 MAPK inhibited MIA-mediated activation of the COX-2 promoter. MIAs stimulated the binding of the activator protein-1 transcription factor complex to the cyclic AMP response element in the COX-2 promoter. A dominant negative form of c-Jun inhibited the activation of the COX-2 promoter by MIAs. Additionally, cytochalasin D, an agent that inhibits actin polymerization, stimulated COX-2 transcription by the same signaling pathway as MIAs. Thus, **microtubule**- or actin-**interfering** agents stimulated MAPK signaling and activator protein-1 activity. This led, in turn, to induction of COX-2 gene expression via the cyclic AMP response element site in the COX-2 promoter.

L25 ANSWER 18 OF 23 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000090794 MEDLINE
DOCUMENT NUMBER: 20090794 PubMed ID: 10623471
TITLE: Microtubule **inhibitors** elicit differential effects on **MAP kinase** (JNK, **ERK**, and p38) signaling pathways in human KB-3 carcinoma cells.
AUTHOR: Stone A A; Chambers T C
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock,

Arkansas, 72205-7199, USA.
CONTRACT NUMBER: CA75577 (NCI)
SOURCE: EXPERIMENTAL CELL RESEARCH, (2000 Jan 10) 254 (1) 110-9.
Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000309
Last Updated on STN: 20000309
Entered Medline: 20000224

AB Microtubule inhibitors are widely used in cancer chemotherapy, but the signaling mechanisms that link microtubule disarray to destructive or protective cellular responses are poorly understood. Because members of the mitogen-activated protein kinase (MAPK) family have been implicated in regulation of cell survival and cell death, we examined the extent and kinetics of activation of JNK, ERK, and p38 MAPKs in response to treatment of KB-3 carcinoma cells with several microtubule inhibitors. All four agents tested (vinblastine, **vincristine**, Taxol, and colchicine) caused significant (6- to 13-fold) activation of JNK, concomitant inactivation of ERK, and a reduction in basal p38 MAPK activity. JNK activation and ERK inactivation occurred prior to caspase 3 activation. The microtubule inhibitors also induced phosphorylation of Raf-1 kinase. SEK-1, upstream of JNK, was also activated and phosphorylated in response to the microtubule inhibitors, and sustained phosphorylation of three endogenous JNK substrates (c-Jun, ATF-2, and JunD) was observed. By comparison, the antitumor agent doxorubicin induced activation of JNK and p38 but had no effect on ERK activity or Raf-1. These data demonstrate that microtubule inhibitors elicit distinct and specific effects on MAPK-mediated signaling pathways and suggest in particular that coordinate and reciprocal alterations in JNK and ERK activities are important facets of the cellular response to microtubule disruption.

L25 ANSWER 19 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:772853 HCAPLUS
DOCUMENT NUMBER: 128:29985
TITLE: Molecular targets of the chemotherapy in lung cancer
AUTHOR(S): Nakamura, Youichi; Saijo, Nagahiro
CORPORATE SOURCE: Med. Oncol. Div., Natl. Cancer Cent. Hosp., Tokyo, 104, Japan
SOURCE: Saishin Igaku (1997), 52(12), 2700-2706
CODEN: SAIGAK; ISSN: 0370-8241
PUBLISHER: Saishin Igakusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 17 refs., on approach to the mol. pharmacol. of lung cancer, discussing cell cycle-targeted tumor inhibitors, e.g., CDDP, **vincristine**, topoisomerase inhibitors, and mitomycin C, and signal transduction system-targeted drugs including **MAP kinase inhibitors**, tyrosine **kinase inhibitors**, Ras protein **inhibitors**, and protein C kinase inhibitors.

L25 ANSWER 20 OF 23 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 97343037 MEDLINE
DOCUMENT NUMBER: 97343037 PubMed ID: 9199666
TITLE: Modulation of protein kinases and **microtubule** -associated proteins and changes in ultrastructure in

female rat pituitary cells: effects of estrogen and bromocriptine.

AUTHOR: Matsuno A; Takekoshi S; Sanno N; Utsunomiya H; Ohsugi Y; Saito N; Kanemitsu H; Tamura A; Nagashima T; Osamura R Y; **Watanabe K**

CORPORATE SOURCE: Department of Neurosurgery, Teikyo University Ichihara Hospital, Chiba, Japan.

SOURCE: JOURNAL OF HISTOCHEMISTRY AND CYTOCHEMISTRY, (1997 Jun) 45 (6) 805-13.
Journal code: 9815334. ISSN: 0022-1554.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970721
Last Updated on STN: 19980206
Entered Medline: 19970710

AB This study focused on the intracellular signal transduction system and **microtubule**-associated proteins (MAPs), such as MAP-2 and Tau protein. The modulation of these proteins and their correlation with ultrastructural changes were investigated in rat pituitary prolactin (PRL) cells. Adult female Wistar rats were treated with estrogen and bromocriptine and their pituitary glands were removed for analysis of the expression of tubulin, MAP-2, Tau protein, protein kinase C (PKC), and calcium calmodulin (CaM) kinase. Western blot analysis showed that estrogen increased and bromocriptine decreased the expression of PKC alpha, beta 1, beta 2, CaM **kinase** alpha, beta, **MAP**-2, and Tau protein. MAP-2 and Tau protein, which are cytosolic proteins, being translated on free ribosomes, were associated with the membrane of whirling rough endoplasmic reticulum (RER) in estrogen-treated cells and dissociated with vesiculated RER induced by bromocriptine. These results suggested that the modulation of MAP-2 and Tau protein may reflect changes of PKC and CaM kinase, and that the quantitative changes and intracellular modulation of MAPs induced by estrogen and bromocriptine, i.e., estrogen-induced association and bromocriptine-induced dissociation of MAP-2 and Tau protein with membrane of RER, may reflect the dynamics of **microtubules** and are associated with structural changes in the RER and changes in the synthesis and intracellular transport of PRL.

L25 ANSWER 21 OF 23 SCISEARCH COPYRIGHT 2003 ISI (R)

ACCESSION NUMBER: 95:556241 SCISEARCH
THE GENUINE ARTICLE: RN965

TITLE: THE ACTIVATION AND NUCLEAR TRANSLOCATION OF EXTRACELLULAR SIGNAL-REGULATED KINASES (**ERK**-1 AND **ERK** -2) APPEAR NOT TO BE REQUIRED FOR ELONGATION OF NEURITES IN PC12D CELLS

AUTHOR: SANO M (Reprint); **KOHNO M**; IWANAGA M
CORPORATE SOURCE: INST DEV RES, AICHI HUMAN SERV CTR, DEPT MORPHOL, KAMIYA CHO, KASUGAI, AICHI 48003, JAPAN (Reprint); GIFU PHARMACEUT UNIV, DEPT BIOL, GIFU 502, JAPAN
COUNTRY OF AUTHOR: JAPAN

SOURCE: BRAIN RESEARCH, (07 AUG 1995) Vol. 688, No. 1-2, pp. 213-218.
ISSN: 0006-8993.

DOCUMENT TYPE: Note; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 23

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The outgrowth of neurites was induced in PC12D cells, a subline of PC12 cells, that were treated not only with NGF but also with dbcAMP, staurosporine or bFGF. Simultaneous activation and rapid nuclear translocation of **MAP kinases** (**ERK**-1 and **ERK**-2) were observed in cells treated with NGF or bFGF. But staurosporine and dbcAMP induced no or only slight activation of the kinases. The nuclear translocation of the **MAP kinases** was not induced by the latter agents. These observations suggest a close relationship between the activation and the nuclear translocation of **MAP kinases** and, moreover, that stimulation and relocalization of **MAP kinases** might not be required for the outgrowth of neurites from PC12D cells. Staurosporine and dbcAMP may stimulate a down-stream step of the NGF pathway, or a parallel pathway(s) to the **MAP kinase** cascade in promoting neurite formation from PC12D cells. These agents mimic the effects of NGF in promoting neurite outgrowth in cultured sympathetic neurons, but not in conventional PC12 cells. Because of the similarity between PC12D cells and primed cells, it seems possible that activation and nuclear translocation of **MAP kinases** might be required for the transcription-dependent differentiation step but might not be necessary for the elongation of neurites at least in response to staurosporine or to dbcAMP.

L25 ANSWER 22 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:119368 HCAPLUS
DOCUMENT NUMBER: 118:119368
TITLE: Mitogen-induced tyrosine-phosphorylated 41kD and 43kD proteins are family members of **MAP kinases**
AUTHOR(S): **Kohno, Michiaki**
CORPORATE SOURCE: Dep. Biol., Gifu Pharm. Univ., Gifu, 502, Japan
SOURCE: Jikken Igaku (1993), 11(1), 30-5
CODEN: JIIGEF; ISSN: 0288-5514
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review, with 18 refs., on the tyrosine phosphorylation of 41 and 43 kDa proteins upon stimulation with epidermal growth factor, platelet-derived growth factor, fibroblast growth factor, 12-O-tetradecanoylphorbol-13-acetate, and tumor necrosis factor. The proteins demonstrate serine/threonine kinase activity toward **microtubule**-assocd. protein 2 and myelin basic protein and are family members of mitogen-activated protein kinases, which are activated by phosphorylation both on tyrosine and threonine residues.

L25 ANSWER 23 OF 23 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 8
ACCESSION NUMBER: 92264863 EMBASE
DOCUMENT NUMBER: 1992264863
TITLE: Mitogen-induced tyrosine-phosphorylated 41- and 43-kDa proteins are family members of extracellular signal-regulated kinases/**microtubule**-associated protein 2 kinases.
AUTHOR: Chatani Y.; Tanaka E.; Tobe K.; Hattori A.; Sato M.; Tamemoto H.; Nishizawa N.; Nomoto H.; Takeya T.; Kadowaki T.; Kasuga M.; **Kohno M.**
CORPORATE SOURCE: Dept. of Biology, Gifu Pharmaceutical University, 5-6-1, Mitahora-higashi,Gifu 502, Japan
SOURCE: Journal of Biological Chemistry, (1992) 267/14 (9911-9916). ISSN: 0021-9258 CODEN: JBCHA3

Search completed by David Schreiber 308-4292

Kam 09/869,916

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Two antipeptide antibodies, one against the peptide corresponding to residues 307-327 (.alpha.Y91) and one against the peptide corresponding to the C- terminal portion (.alpha.C92) of the deduced amino acid sequence of the extracellular signal-regulated kinase 1 (**ERK1**), precipitated two 41-kDa and/or two 43-kDa phosphoproteins from mitogen-stimulated Swiss 3T3 cells. Electrophoretic mobilities on two-dimensional gels of the immunoprecipitated 41- and 43-kDa phosphoproteins were similar to those of the 41- and 43-kDa cytosol proteins, whose increased tyrosine phosphorylation we and others had originally identified in various mitogen-stimulated cells (Cooper, J. A., Sefton, B. M., and Hunter, T. (1984) Mol. Cell. Biol. 4, 30-37; Kohno, M. (1985) J. Biol. Chem. 260, 1771-1779); phosphopeptide map analysis revealed that they were respectively identical molecules. All those phosphoproteins contained phosphotyrosine, and the more acidic forms contained additional phosphothreonine. Immunoprecipitated 41- and 43-kDa phosphoproteins had serine/threonine kinase activity toward myelin basic protein (MBP) and microtuble-associated protein 2 (MAP2). With the combination of two-dimensional gel electrophoresis and the kinase assay in MBP-containing polyacrylamide gels of the .alpha.Y91 immunoprecipitates, with or without phosphatase 2A treatment, we showed that only their acidic forms were active. These results clearly indicate that 41- and 43-kDa proteins, the increased tyrosine phosphorylation of which is rapidly and commonly induced by mitogen stimulation of fibroblasts, are family members of **ERKs**/MAP2 kinases and that phosphorylation both on tyrosine and threonine residues is necessary for their activation.